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Is the Freeman-Tukey double arcsine transformation a reliable approach for proportion meta-analysis ?

An example with a Living SR on Covid-19 vaccines and Pregnancy outcomes.

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Trusted evidence.
Informed decisions.
Better health.

No conflicts of interest

Previous work

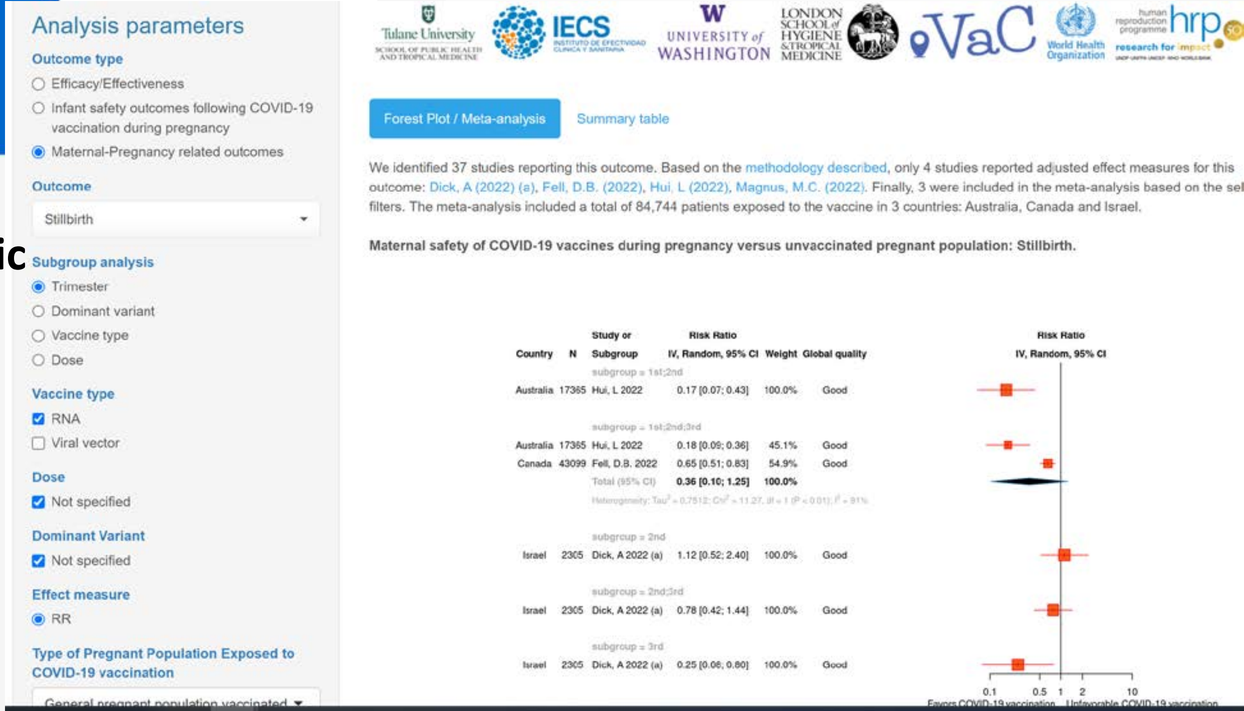
Recently questioned…

- Meta-analysis often utilizes pooling of proportions to gain more accurate estimates of disease frequency, such as cumulative incidence or prevalence. They are usually based on transformed proportions using Freeman-Tukey double arcsine transformations (FTT).
- A recent study proposed the use of generalized linear mixed models (GLMM) over FTT, on the premise the latter produces misleading results, sparking controversy.[1]
- However, other authors, using the same set of studies, reanalyzed the data and concluded that the FTT is the most reliable approach and remains the preferred transformation in proportion meta-analysis.[2]
- We aimed to compare the performance of FTT with GLMM in a large set of proportion meta-analyses from an ongoing Living Systematic Review.

1. Schwarzer G, Chemaitelly H, Abu-Raddad LJ, Rücker G. Seriously misleading results using inverse of Freeman-Tukey double arcsine transformation in meta-analysis of single proportions. Res Synth Methods. 2019;10: 476–483.
2. Doi SA, Xu C. The Freeman-Tukey double arcsine transformation for the meta-analysis of proportions: Recent criticisms were seriously misleading. J Evid Based Med. 2021;14: 259–261.

COVID 19 vaccines for pregnant persons: a living systematic review and meta-analysis

https://safeinpregnancy.org/lsr/



Methdos

- We conducted GLMM[1] and FTT over a **large dataset** of proportions **from a living systematic review** and meta-analysis about **safety, immunogenicity, and effectiveness of COVID-19 vaccines** for pregnant people (https://safeinpregnancy.org/lsr/) applying recommended safeguards (using corrected statistical packages: Metan in Stata) and other approaches (GLMM and Metaprop in R):

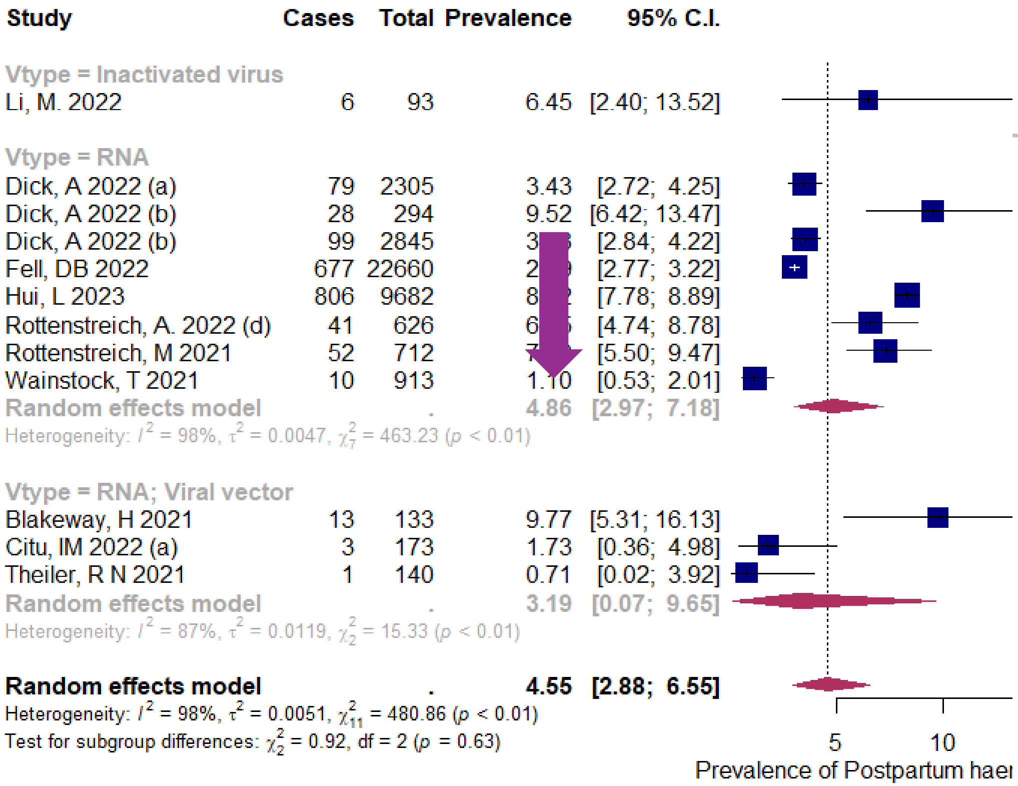
  Safeguards:

  a) avoiding the use of the average of the double arcsine and its variance for synthesis;
  b) using the inverse of the variance of the pooled FTT proportion
  c) modifying the confidence intervals to prevent numerical inaccuracies.

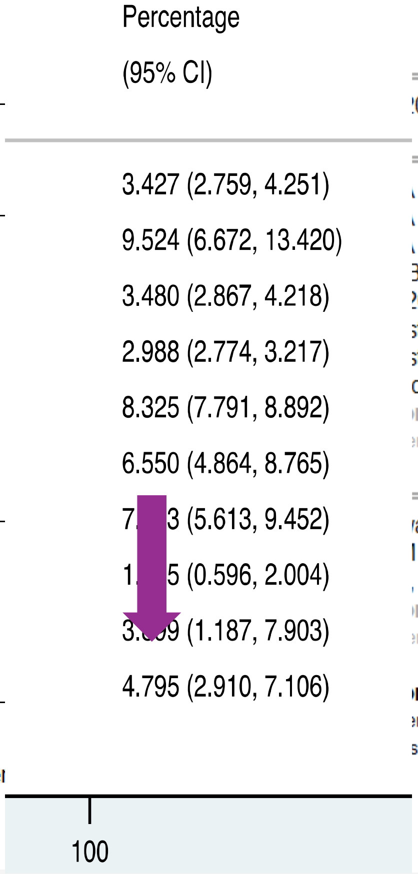
- Compared results for MAs with few/several studies, and for Vaccine outcomes/Adverse effects

Postpartum Hemorrhage

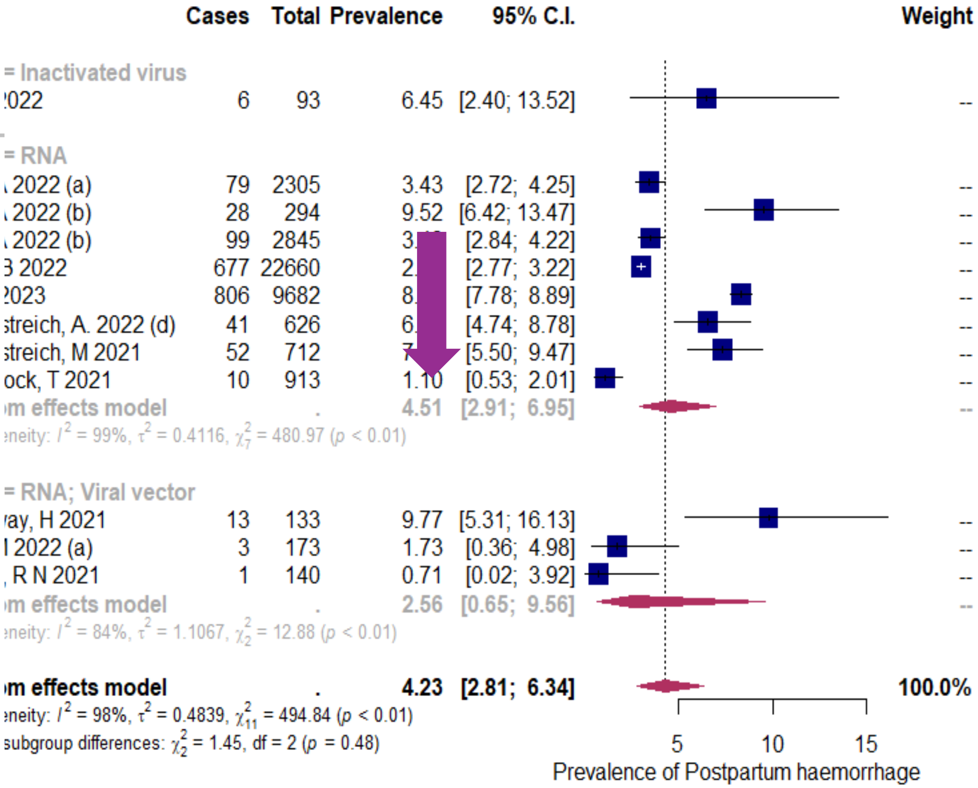
FTT (Metaprop R)



Metan (metan [corr], Stata)



GLMM



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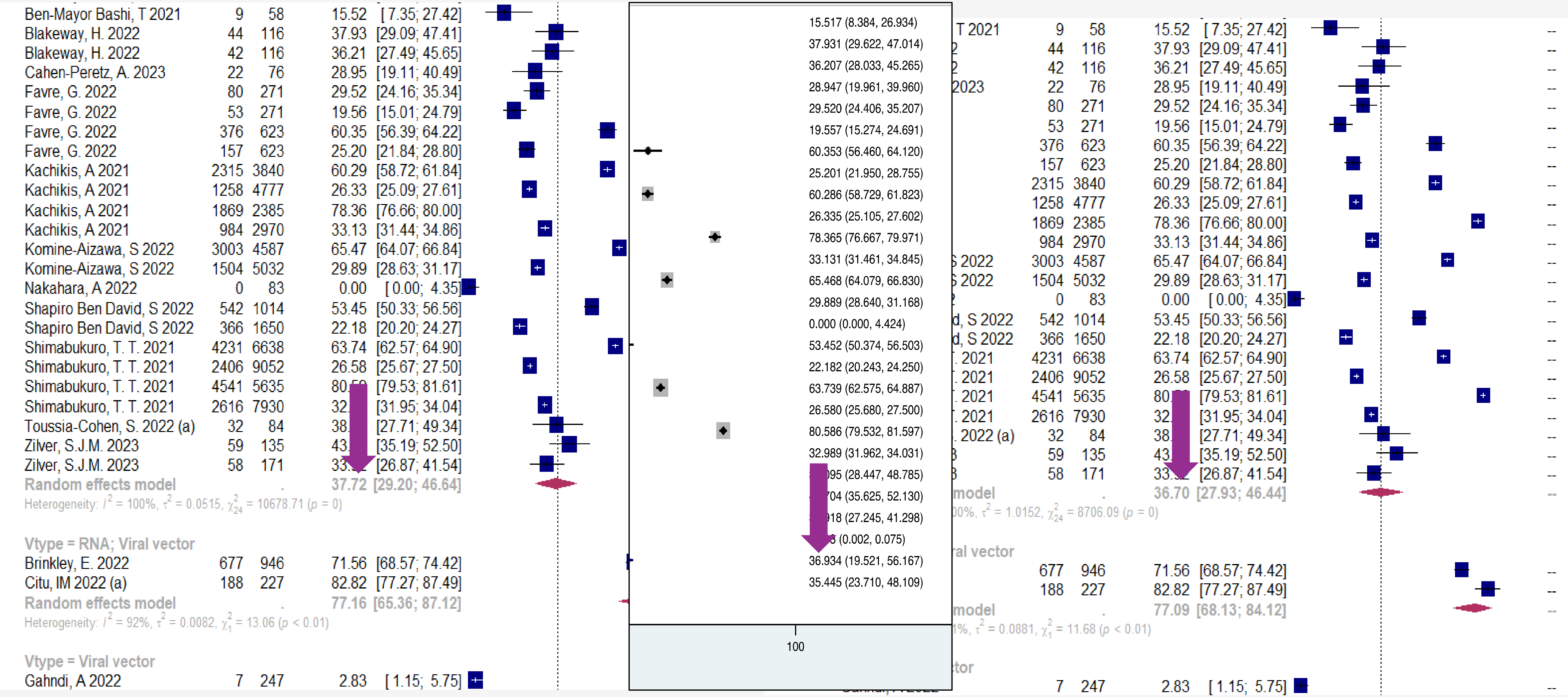
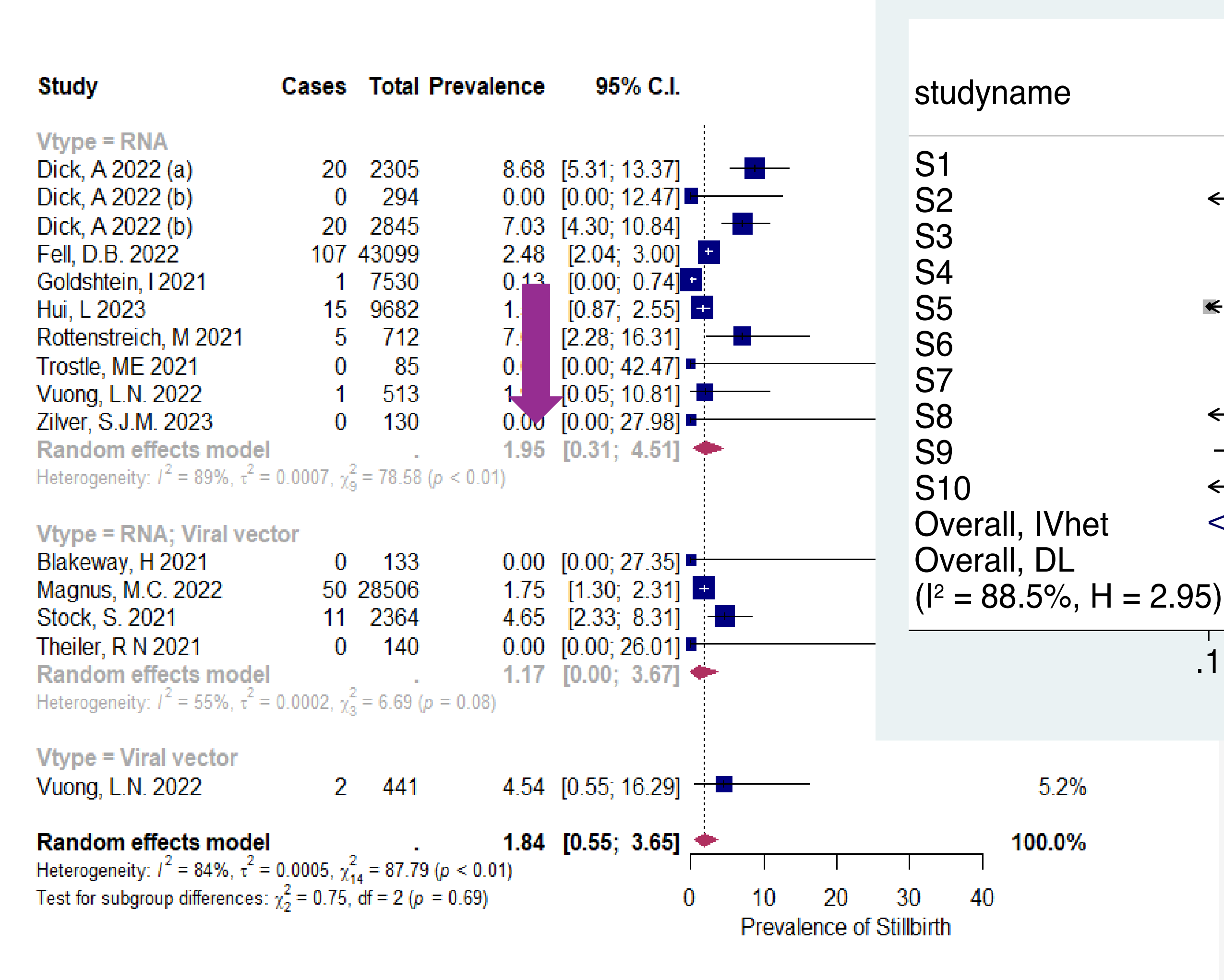
Fatigue

FTT (Metaprop R) | Metan (metan [corr], Stata) | GLMM, R

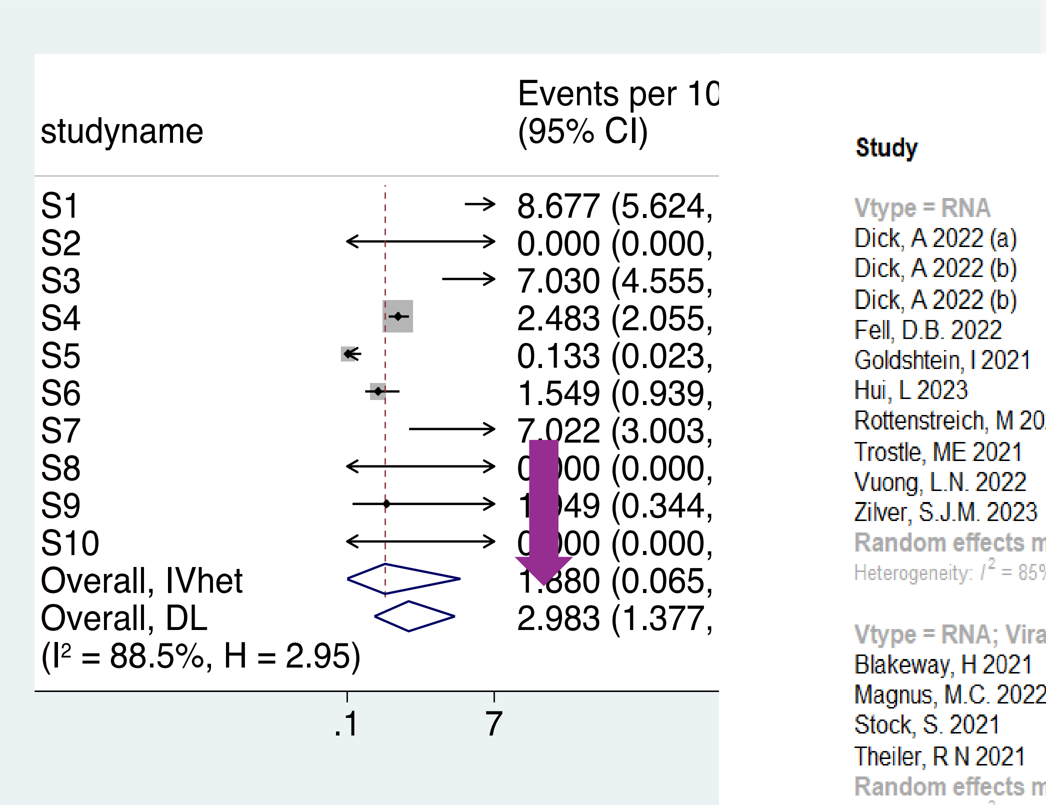


Stillbirth

FTT (metaprop, R)



Metan (metan [corr], Stata)



GLMM (R)

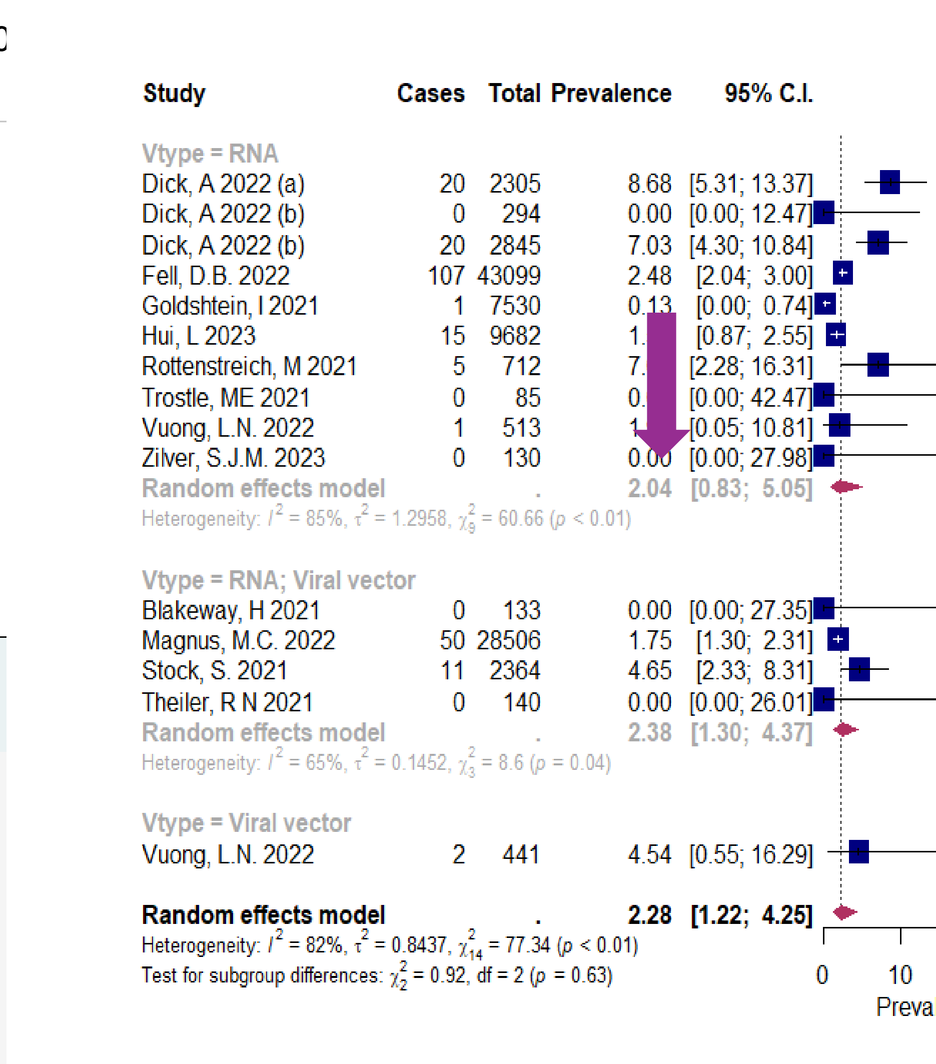


Table. Summary of MA results per vaccine type subgroup considering FTT and GLMM aproaches

Outcome	Subgroup	#studies	FTT				GLMM				Rel Diff (%)	Abs Diff
			prop	Prop-95% CI	I²%	I²%-95% CI	prop	Prop-95% CI	I²%	I²%-95% CI		
PPH	Inactivated virus	1	6.450	[2.20; 12.50]	NA	NA	6.450	[2.93; 13.62]	NA	NA		
	RNA	8	**4.860**	[2.97; 7.18]	98.49	[97.95;98.89]	**4.510**	[2.91; 6.95]	98.54	[98.03;98.92]	7.20	**0.350**
	RNA; Viral vector	3	3.190	[0.07; 9.65]	86.95	[62.75;95.43]	2.560	[0.65; 9.56]	84.47	[53.74;94.79]	19.75	0.630
Stillbirth	RNA	10	**1.945**	[0.307; 4.512]	88.55	[81.03;93.09]	**2.045**	[0.826; 5.053]	85.16	[74.47;91.38]	5.14	**0.100**
	RNA; Viral vector	4	1.172	[0.001; 3.671]	55.16	[0.00;85.16]	2.380	[1.296; 4.366]	65.11	[0.00;88.15]	103.07	1.208
	Viral vector	1	4.535	[0.068; 13.620]	NA	NA	4.535	[1.135; 17.946]	NA	NA		
Fatigue	RNA	25	**37.720**	[29.20; 46.64]	99.78	[99.76;99.79]	**36.700**	[27.93; 46.44]	99.72	[99.70;99.75]	2.70	**1.020**
	RNA; Viral vector	2	77.160	[65.36; 87.12]	92.34	[73.92;97.75]	77.090	[68.13; 84.12]	91.44	[69.92;97.56]	0.09	0.070
	Viral vector	1	2.830	[1.07; 5.33]	NA	NA	2.830	[1.36; 5.82]	NA	NA		
Apgar score<7 at five minutes	RNA	13	1.260	[0.76; 1.88]	89.38	[83.68;93.09]	1.210	[0.76; 1.91]	80.21	[67.02;88.13]	3.97	0.050
	RNA; Viral vector	3	1.310	[1.17; 1.45]	0.00	[0.00;89.60]	1.510	[1.37; 1.65]	0.00	[0.00;89.60]	15.27	0.200
SAEs	RNA	5	0.254	[0.129; 0.407]	0.00	[0.00;79.20]	0.559	[0.424; 0.737]	0.00	[0.00;79.20]	120.07	0.305
	Viral vector	1	0.405	[0.000; 1.731]	NA	NA	0.405	[0.057; 2.816]	NA	NA		

Conclusions

- We compared methods across different type of outcomes in studies about COVID-19 vaccination in pregnant persons
- FTT continues to be the a valid method under new implementations of statistical software.
- Ensuring the optimal method for conducting meta-analyses of proportions is essential, as it plays a pivotal role in making accurate estimations in epidemiology and guiding decision-making processes.

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Thank You!